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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NICKOL, GARY B	

ART UNIT	PAPER NUMBER
1642	15

DATE MAILED: 03/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/849,115	KOZAROV ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,11-16 and 21-29* is/are pending in the application.

4a) Of the above claim(s) *21-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 11-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8,9,12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The response filed on December 30, 2002 (Paper No. 14) to the restriction requirement of November 27, 2002 has been received. Applicants have elected Group I, claims 1-5, 11-16 for examination and have also elected the species "carcinoma" and "HagA". Because applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a).

Claims 21-29 were added.

Claims 1-5, 11-16, and 21-29 are pending.

Claims 21-29 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-5, and 11-16 are pending and are currently under examination.

Specification

The brief description of the figures (Figures 13a-e & 14a-d) on pages 8-9 are objected to because the descriptions do not indicate what the arrows are pointing to and/or represent. For example, see Figure 13d. Applicant should amend the specification to indicate what the arrows are pointing to, and Applicant is reminded that no new matter can be included with the response.

Claim Objections

Claims 5 and 16 objected to for reciting "DNA" which is drawn to a non-elected invention. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is vague for reciting "other cysteine protease". What other cysteine protease? It is not clear what applicant is referring to, and the specification does not appear to mention "other cysteine protease" with regards to the claimed method.

Also, Claim 5 recites the limitation said "protease". There is insufficient antecedent basis for this limitation from which claim 5 depends.

Claim 16 is vague for reciting "other proteinase". What other proteinase? It is not clear what other proteinase applicant is referring to, and the specification does not appear to contemplate "other proteinase". Also, such a recitation appears to lack antecedent basis since the claim refers to "said protease", not proteinase.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 11-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to methods for treating or preventing an angioproliferative condition comprising administering to a patient a pharmaceutically effective amount of a proteinase or protease derived from *Porphyromonas gingivalis* such as Hemagglutinin A (HagA) wherein the angioproliferative condition includes such diseases as cancers (i.e. carcinomas, sarcomas, or melanomas).

With regards to the treatment of cancer conditions, the specification teaches (page 5, line 16) that the method of treating cancer utilizes *P. gingivalis* derived proteolytic compounds to inhibit angiogenesis associated with malignant tumor proliferation by disrupting endothelial layer cell-cell and cell-matrix adhesion bonds. The specification further teaches (page 11, lines 10+) that the present inventors have discovered that, surprisingly, sequences derived from or related to *P. gingivalis* may be used to treat or prevent angioproliferative disorders, including but not limited to melanoma, sarcoma, and carcinomas of the breast, colon, lung and prostate. The specification also includes certain in-vitro experiments illustrating the percent detachment of

active and quiescent HUVEC cells or active and quiescent human non-small cell lung carcinoma cells from a carcinoma cell line following treatment with a protein extract from *P. gingivalis*.

However, the claims are not enabled because the specification does not provide sufficient guidance and objective evidence that the claimed method would predictably treat or prevent an angioproliferative condition such as a carcinoma.

Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in-vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather

skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer also teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Moreover, Eckhardt *et al.* (Annals of Oncology, Vol. 7, 1996, IDS), in a phase I clinical trial, teach that there were no complete or partial tumor responses (page 494, 1st column) with tecogalan sodium, a proteinase derived from a bacterium even though the drug has shown efficacy in-vitro as an anti-angiogenic agent (page 491, 2nd column). Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

As drawn to inhibiting angiogenesis in the vasculature of a patient suffering from cancer, Zeeter (Annu. Rev. Med., 1998, v49. Pp. 407-24,) teaches that anti-angiogenic treatment can reduce a tumor mass back to its avascular size, but it may not completely eliminate tumors that regress to sizes no longer dependent on increased vascularity (page 417, 2nd column, last paragraph). Thus, the potential for in-vivo micrometastasis is not eliminated. Also, the current state of the art on the latest in-vivo testing of anti-angiogenic drugs have been mixed. For example, it was recently revealed that the drug Endostatin is unlikely to be the kind of across-

the-board cancer cure that many had hoped for. Out of the 61 terminally ill patients tested, not one recovery had been seen (MSNBC News Services, "Mixed results on new cancer drug", November 9, 2000). Hence, it would not be predictable that a method drawn to inhibiting an angioproliferative condition would be effective in a patient suffering from cancer. Further, the treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

Lastly, with regards to "prevention", reasonable guidance with respect to preventing any cancer must rely on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid

preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease.

For the above reasons, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, and 11-14, 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Sasisekharan *et al.* (US Patent No. 5,567,417; October 1996).

Sasisekharan *et al.* teach a method for treatment or prevention of an angioproliferative condition which comprises administering to a patient experiencing said angioproliferative conditional a pharmaceutically effective amount of a proteinase (column 3, lines 35+) (The specification refers to a proteinase as a protein, page 10, line 1.) to exert an angiostatic effect wherein said angioproliferative condition is a carcinoma (column 18, lines 8 and 26), wherein said proteinase is derived from a bacterium (column 5). Sasisekharan *et al.* also teach a method for selectively treating an angioproliferative condition which comprises contacting a vasculature supplying a biological structure affected by said angioproliferative condition with an angiostatically effective amount of a protease wherein said angioproliferative condition is a carcinoma, wherein said protease is derived from a bacterium and wherein said protease is a

"other proteinase". Though the prior art does not specifically teach a protease *per se* (i.e., the prior art teaches heparinases that cleave sugar bonds, see column 3, line 33), the specification does not appear to limit what is included or excluded as a protease- only that it *includes* any proteolytic activity and that the term "protease" is intended to imply the ability of an enzyme, natural or recombinant, to disrupt cell-cell adhesion and cell-matrix adhesion bonds, particularly in the vasculature, but also in the tumor mass (specification, page 10, lines 24-28). Furthermore, since heparin-like molecules are associated with membrane proteins (referred to collectively as proteoglycans, see column 2, lines 47+) found predominantly in the extracellular matrix and function in cell adhesion to the extracellular matrix, heparinase activity would include the disruption of cell-matrix adhesion bonds. Furthermore, although the prior art does not specifically teach that the basolateral surface of the vasculature is contacted with the protease, the prior art does teach that heparinase III acts at the more "heparan sulfate-like regions" of the endothelial cell polysaccharide (column 5, line 1) wherein heparan sulfate, which is chemically almost indistinguishable from heparin, is believed to be present on virtually all cell surfaces (column 2, lines 47+). Also see Table I, page 12 wherein heparinases were added to a capillary endothelial cell proliferation assay. Thus, inherently, the protease would contact the basolateral surface of the vasculature which includes endothelial cell surfaces.

Claims 1-2, 5 and 11-13, 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Holaday *et al.* (WO 99/60984; December 1999, IDS).

Holaday *et al.* teach a method for treatment or prevention of an angioproliferative condition which comprises administering to a patient experiencing said angioproliferative

conditional a pharmaceutically effective amount of a serine protease to exert an angiostatic effect wherein said angioproliferative condition is a carcinoma, . Holaday *et al.* also teach a method for selectively treating an angioproliferative condition which comprises contacting a vasculature supplying a biological structure affected by said angioproliferative condition with an angiostatically effective amount of a protease wherein said angioproliferative condition is a carcinoma, wherein said protease is a "other proteinase". (see abstract, page 7). Furthermore, since the serine protease (i.e. PSA) is an endothelial cell-specific inhibitor of angiogenesis (pages 14-15), inherently the basolateral surface of the vasculature is contacted with the protease.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
March 5, 2003